REMARKS

Claims 1-4 and 7-21 were examined in the Office Action mailed July 2, 2004 (the "Office Action"). Claim 1 is objected to based on a misspelling of the word "expression." Claim 10 is objected to under 37 CFR 1.75(c) as being in improper dependent form for failing to limit the subject matter of a previous claim. Claims 1-4 and 7-21 are rejected under the enablement requirement of 35 U.S.C. § 112, first paragraph. Claim 16 stands rejected under 35 U.S.C. § 102(e) as being anticipated by Li (U.S. Pat. Pub. No. 2002/0177222). Claims 3, 4, 7, 8, 10 and 15-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Russell et al. (U.S. Pat. No. 6,156,303) taken with Matsushita et al. (*Gene Therapy* (1998) 5, 938-45), and claims 1-4, 7-11 and 15-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over High et al. (U.S. Pat. No. 6,039,392) taken with Matsushita et al. (1998).

These rejections are believed to be overcome in part by amendments, and are otherwise traversed for the reasons discussed below. To enhance precision, specific passages within the specification are referred to herein by the paragraph numbering in the publication of the instant application (U.S. Patent Application Publication No. 2002/0159978).

AMENDMENTS TO THE CLAIMS

Claim 1 has been amended for several reasons. Two amendments correct typographical errors, i.e. the spellings of "virions" and "expression." Other amendments to Claim 1 replace treatment of hemophilia in the preamble with

expression of Factor IX, and delete reference to Factor IX expression at levels having a therapeutic effect, the effect being an increase in blood clotting efficiency in the mammal. Claim 1 has also been amended for clarity.

Claims 3 and 16 have been amended to delete reference to expression of said heterologous nucleic acid to provide a therapeutic effect, and for clarity. Claim 12 has been amended for clarity. Claims 10 and 15 have been canceled, and claim 11 has been amended to depend from claim 3 rather than canceled claim 10.

None of the amendments adds new matter.

OBJECTIONS TO THE CLAIMS

Claim 1 was objected to for misspelling of the word "expression." Claim 1 has been amended to correct that error, and also to correct a typographical error in the spelling of the word "virions."

Claim 10 was objected to under 37 CFR 1.75(c) as being in improper dependent form for failing to limit the subject matter of a previous claim. Claim 10 has been canceled.

In light of these amendments, applicant respectfully requests withdrawal of the above referenced objections to the claims.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-4 and 7-21 were rejected for failure to comply with the enablement requirement of 35 U.S.C. §112, first paragraph. The Examiner argues that

> [T]he specification, while being enabling for a method for treating hemophilia in a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid encoding factor IX protein operably linked to expression control elements is directly administered to at least one muscle cell in the mammal, does not reasonably provide enablement for a method of gene therapy comprising administering at least one rAAV comprising an AAV-6 capsid and a heterologous nucleic acid operably linked to expression control elements to at least one muscle cell using a genus of administration routes, whereby expression of said nucleic acid provides for a therapeutic effect.

Office Action at p. 3. With regard to the asserted lack of enablement, applicant respectfully disagrees.

The test of enablement is not whether applicant has demonstrated success with every conceivable embodiment of the invention. Rather, the test is whether one of skill in the art could practice the claimed invention without undue experimentation. Unless the Examiner establishes "adequate reasons" as to why a person of skill in the art could not use the genus as a whole, representative examples are sufficient:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

MPEP § 2164.02.

Furthermore, "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." MPEP § 2164.08, citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). A considerable amount of experimentation is permissible, if such experimentation is routine and/or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.01 ("The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.")

The passage of the Office Action quoted above seeks to limit the claims to a disclosed embodiment by implying that nothing beyond the specific examples in the specification is enabled. However, "because only an enabling disclosure is required, applicant need not describe all actual embodiments," and "even in unpredictable arts, a disclosure of every operable species is not required." MPEP §§ 2164.02, 2164.03. Furthermore, an applicant may claim more broadly than his preferred embodiments:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976); MPEP § 2164.08.

Nevertheless, solely in order to advance prosecution, applicant has amended the claims to no longer require the treatment of any specific disease or the expression of a heterologous nucleic acid to provide a therapeutic effect. As

amended, claim 16 (and associated dependent claims) is directed to a method of expression of a heterologous nucleic acid in a mammal, and claim 1 is directed to expression of Factor IX in at least one muscle cell of a mammalian subject. As amended, claim 3 (and associated dependent claims) is directed to delivery of a heterologous nucleic acid to at least one muscle cell in a mammalian subject.

The specification discloses that methods of the instant invention may be used for reasons other than treating a disease, for example to deliver a heterologous nucleic acid sequence to a host cell to help elucidate its physiological or biochemical function, including the generation of experimental animals, e.g. transgenic mice. Application at ¶¶ 0037-40. For example, a method of the instant invention may be used to over-express or "knock out" (e.g. by antisense RNA) a specific gene in an experimental animal. Application at ¶¶ 0038-39. Such experimental animals may also be used to study the pharmaco- and toxico-kinetics of potential therapeutic agents or methods. Application at ¶ 0042.

The specification contains examples of delivery and expression of a heterologous nucleic acid (encoding Factor IX) in mice, in dogs, and in humans. *See* Application, Examples 2-4. Data are also presented demonstrating successful delivery and expression of Factor IX in both mice and dogs. *See* Application, Examples 2-3 and FIG. 1. Delivery and expression of other heterologous nucleic acids may be accomplished using standard methods known to those of skill in the art using rAAV-6 expression vectors analogous to those described in detail for delivery and expression of Factor IX. Such standard

methods include cloning a gene fragment into an AAV-derived vector DNA, preparation of rAAV virions, and transfection into a cell.

Applicant respectfully disagrees with the argument that one of skill in the art could not readily determine how to select and use suitable nucleotide sequences for a given disease. Office Action at p. 13. The level of skill in the art of molecular biology is high, and one of skill in the art would know of public databases (e.g. Genbank) that contain sequences for a number of disease-related genes. Genbank can be searched, for example, through the internet website of the National Library of Medicine (Entrez) at the following internet address: www.ncbi.nlm.nih.gov/entrez. For example, one of skill in the art could use the list of disease states and genes provided at paragraph 0032 of the specification to obtain nucleic acid sequences for heterologous nucleic acids to be delivered and expressed using the methods and rAAV-6 vectors of the present invention. Genbank contains genomic sequences, cDNA sequences and protein sequences for many disease-related genes. With regard to other potential genes for other disease states, the Online Mendelian Inheritance in Man (OMIM) database (accessible via the same Entrez website) can be used to determine additional genes believed to be involved in various disease states.

The Office Action asserts that the art of record teaches problems with using rAAV in gene therapy, listing three proteins whose full-length genes are too long to be packaged in an rAAV virion. Although applicants are not required to show enablement of every species, as of the filing date of the application at least one of the listed genes (Factor VIII) had already been delivered using an rAAV

vector, albeit not as the full-length gene. *See* WO 00/23116, FIGS. 1 and 2. To that extent that some other potential genes or gene fragments would be too long to be delivered and expressed using methods of the present invention, undue experimentation would not be required since simple inspection of the length of the gene sequence would reveal to one of skill in the art whether it is too long to be delivered in an rAAV vector.

In addition, as pointed out in applicant's May 6, 2004 Response to Office Action (at pp. 9-10), a number of other genes have in fact been delivered and expressed using rAAV vectors, despite the known vector size limitation, including VEGF-A (Galeano et al., *Diabetalogia* (2003) 46:546-555), hAAT (Song et al., *Gene Therapy* (2004) 11:181-186), GUSB (Skorupa et al., *Experimental Neurology* (1999) 160:17-27), PAH (Mochizuki et al., *Gene Therapy* (2004) 1-6) and IL-1ra (Tsai et al., *Molecular Neurosciences* (2003) 14(6):803-807). These references demonstrate that the vector size limit does not prevent use of rAAV vectors for delivery and expression of a wide variety of genes. To the extent that the Examiner's argument is that the AAV vector size limitation creates an excessive number of inoperable embodiments, thus rendering the claims nonenabled, the references listed above refute that argument by demonstrating that rAAV vectors are inherently capable of delivering and expressing a number of genes.

In any event, the three genes listed represent only a fraction of the over 40 genes listed at paragraphs 0032-0033 of the publication of the instant application, and an even smaller fraction of all potential genes. The presence of

a small number of inoperative embodiments within the scope of a claim does not necessarily render the claim nonenabled. M.P.E.P. § 2164.08(B). *See also Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

Applicant reiterates his disagreement with the Examiner's assertion that the specification does not teach how to use any other route of administration other than intramuscular. Office Action at pp. 6-7, 10. Paragraph 0034 of the publication of the instant application discloses the use of isolated limb perfusion for delivery of rAAV-6 virions to a mammalian subject. U.S. Pat. No. 6,177,403 is cited and incorporated by reference to provide an enabling disclosure of a variant of the isolated limb perfusion (*i.e.* intravascular) delivery technique. With regard to the argument that the specification does not teach one skilled in the art how to administer a sufficient amount of rAAV using delivery methods other than intramuscular administration (Office Action at p. 10), the selection of an optimal dose is dependent on a number of factors and it is within the skill in the art to determine the proper dosage, as disclosed at paragraph 0035 of the instant application. Dosage can be determined by reference to such factors as the route of administration, the desired level of expression, the specific disease state, the host immune response to rAAV or to the gene product, and the stability of the gene product. Dosage may also be determined based on animal results or human clinical trials. Such routine experimentation is not "undue," and thus does not render the claims nonenabled.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with the information known in the art without undue experimentation. *Ex Parte Froman*, 230 USPQ 546 (BPAI 1986). In fact, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance. *Ex Parte Froman*, *supra*; *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In order to practice the claimed invention using a gene other than Factor IX, a person of skill in the art armed with the name of a candidate gene (for example on of the genes provided in the list in the specification) would have to obtain the sequence of the gene, for example using Genbank, and clone that sequence into a vector analogous to the Factor IX vector disclosed in the specification. Simple inspection of the length of the gene sequence would reveal whether it is too long to be delivered in an rAAV vector. The vector could then be prepared and administered as disclosed in detail for Factor IX vectors in the specification. There would be a reasonable expectation of success because the specification demonstrates that Factor IX is delivered and expressed from an rAAV-6 vector using methods of the instant invention, and there is no reason to suspect that a different heterologous nucleic acid sequence would not also be delivered and expressed using those same vectors and methods.

There is no objective reason of record that would indicate that those skilled in the art as of the filing date of the application would doubt that applicant's methods would be equally useful in delivering and expressing a

different heterologous nucleic acid sequence given that the method is demonstrated to successfully deliver and express a sequence encoding Factor IX. Section 112 requires nothing more than objective enablement. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). In light of the amendments to the claims, and the arguments presented above, applicant respectfully requests withdrawal of the rejections of Claims 1-4 and 7-21 under 35 U.S.C. § 112, first paragraph, and thus prompt allowance of claims 12-14 and 19-21.

REJECTIONS UNDER 35 U.S.C. §§102(e) AND 103(a)

Anticipation

Claim 16 was rejected under 35 U.S.C. §102(e) as being anticipated by Li (U.S. Pat. Pub. No. 2002/0177222). Although the Examiner notes that "Li teaches production of wild type free recombinant AAV virions (rAAV)," the absence of wild-type AAV is not a limitation of any of the pending claims.

It is well established that to anticipate, a prior art reference must be enabling, thus placing the allegedly disclosed subject matter in the possession of the public. *Akzo N.V. v. United States ITC*, 1 USPQ2d 1241 (Fed. Cir. 1986); *Ashland Oil, Inc. v. Delta Resins & Refracs., Inc.*, 227 USPQ2d 657 (Fed. Cir. 1985); *Reading & Bates Constr. Co. v. Baker Energy Res. Corp.*, 223 USPQ 1168 (Fed. Cir. 1984). Li fails to enable preparations of rAAV vectors lacking the components necessary to form replication competent adenovirus. To be enabling a reference must teach one reasonably skilled in the art how to make and use the invention without undue experimentation. In considering whether the

required experimentation would be undue, the Examiner should assess, among other things, (1) the direction provided in the disclosure, (2) the nature of the invention, and (3) the quantity of experimentation needed to make or use the invention based on the contents of the disclosure. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

As illustrated in Examples 2, 3, 5, and graphically in FIGS. 1-3B, Li uses adenovirus helper in the production of rAAV vectors, and "amplified adenovirus helper" is among the products. Although Li refers to "accessory function vectors" and "adenovirus free rAAV virions" (¶ 0011), there is no disclosure, nor any citation incorporated by reference, to enable production of a preparation of rAAV virions lacking the components necessary to form replication competent adenovirus. One of skill in the art, armed with only the Li patent, would be forced to engage in undue experimentation to devise an "accessory function vector" that is otherwise not described in the specification. Li presents, at most, the suggestion that such a vector may be possible, but not how to make or use it.

In addition, Li discloses AAV-6 only as one member in as list of AAV serotypes (¶¶ 0044, 0071). Although other paragraphs recite that various components of the AAV transduction system "can be derived from any viral serotype," no guidance is provided for use of AAV-6.

To anticipate a claim a single source must contain all elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 USPQ 81, 90 (Fed. Cir. 1986). Because Li does not provide and enabling disclosure for producing a preparation of rAAV virions lacking the components

necessary to form replication competent adenovirus, it does not anticipate claim 16. Therefore, applicant requests withdrawal of the anticipation rejection of claim 16 under 35 U.S.C. §102(e).

Obviousness

Claims 3, 4, 7, 8, 10 and 15-17 were rejected under 35 U.S.C. §103(a) as obvious in light of Russell et al. (U.S. Pat. No. 6,156,303) taken with Matsushita et al. (*Gene Therapy* (1998) 5: 938-45), and claims 1-4, 7-11 and 15-18 were rejected as being obvious in light of High et al. (U.S. Pat. No. 6,039,392) taken with Matsushita et al. (1998). Applicant traverses.

Russell et al. is characterized as teaching use of AAV-6 comprising a heterologous nucleic acid sequence to treat a pathologic condition in a mammal, including blood clotting disorders and delivery to muscle cells. Office Action at p. 15. Matsushita et al. is characterized as teaching the production of rAAV vectors without use of helper virus.

M.P.E.P. § 2142 provides that in order to establish a *prima facie* case of obviousness, three general criteria must be met. First, there must be some suggestion or motivation, either in the references themselves of in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Unexpected results provide objective evidence of nonobviousness. *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988); *Lindemann Maschinefabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984) ("unexpected results may be strong support for a conclusion of nonobviousness"). Evidence of unexpected results includes art that teaches away from the claimed invention. *Id.* A biologically active agent that is significantly more active than expected is another example of an unexpected result supporting a finding of nonobviousness. *Ex Parte A*, 17 U.S.P.Q.2d 1716 (BPAI 1990).

One factor to be considered in a determination of obviousness is whether the prior art teaches away from the claimed invention. *Specialty Composites*, 845 F.2d at 991. Inspection of FIG. 5 of Russell et al. indicates that AAV-6 vectors give lower levels of expression of alkaline phosphatase than AAV-2 vectors in all six cell lines examined. One of skill in the art would conclude, based on these data, that AAV-6 should not be used to deliver and express heterologous nucleic acid sequences. However, as shown in FIG. 1 of the instant application, and discussed at paragraph 0043, rAAV-6-hF.IX virions provide 32-fold higher serum levels of hF.IX in mice than rAAV-2-hF.IX virions at three weeks post-administration. At seven weeks post administration the difference was less dramatic, but mice treated with rAAV-6 vectors still have significantly higher serum levels of FIX than those treated with rAAV-2 vectors. Because Russell et al. teaches away from the use of AAV-6, it does not render

obvious the claims of the instant application, which are all directed to use of those same apparently inferior AAV-6 vectors.

High et al. is characterized as teaching use of rAAV vectors (including AAV-6) encoding Factor IX (including human Factor IX) to treat hemophilia in a mammal, including operable linkage to an expression control unit and administration to muscle (including skeletal muscle). Matsushita et al. is characterized as teaching the production of rAAV vectors without use of helper virus.

As discussed in applicant's May 6, 2004 Response to Office Action (at p. 13), the results presented in the specification of the instant application show unexpected levels of Factor IX expression when compared to the levels reported in High et al. Specifically, High et al. discloses an expression level plateau of 200 to 350 ng hF.IX/ml of mouse plasma five to seven weeks following injection of $2X10^{11}$ viral vector genomes (vg)/**mouse**. High et al., col. 16, ll. 53-59. The level of expression was three to four fold lower when the dosage was reduced to $2X10^{10}$ vg/mouse. High et al., col. 16, ll. 61-64.

In contrast, applicant's results using rAAV-6 gene delivery show circulating plasma concentrations of hF.IX of 185 ng/ml and 190 ng/ml Factor IX in mouse plasma at three and seven weeks post injection, respectively, using a dosage of $2X10^{11}$ vg/**kg**. Application at Example 2 (¶ 0056). Based on an average mouse size of about 25 g, applicant's method achieved nearly equivalent expression of hF.IX at approximately 1/40 of the dose used in High et al. ($2X10^{11}$ vg/kg $\cong$ $5X10^{9}$ vg/mouse).

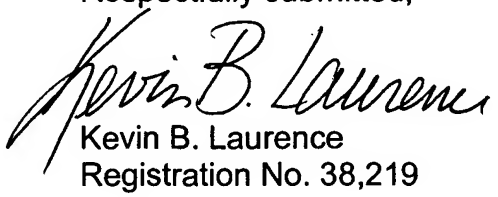
The unexpectedly high level of hF.IX expression achieved using the methods of the instant invention prove that the claimed invention is not obvious in light of High et al. As discussed above, results disclosed in the instant application also show unexpectedly higher levels of expression using rAAV-6 gene delivery, as compared to rAAV-2 delivery, than would be expected based on the disclosure of Russell et al. Accordingly, withdrawal of the rejections of claims 1-4, 7-11 and 15-18 as obvious under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

For the reasons discussed above, applicant submits that claims 1-4 and 7-21 are in proper condition for allowance, and a Notice of Allowance is respectfully requested. If the Examiner notes any further matters which he believes may be resolved by a telephone interview, he is encouraged to contact M. Christina Thomson, J.D., by telephone at 510-748-7208.

DATE: January 3, 2004

Respectfully submitted,



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